J. Org. Chem. **2000,** *65,* 1629−1635

New Insights into the Chemistry of Lithium Carbamoyls: Characterization of an Adduct ($R_2NC(O)CLi(OLi)NR_2$)

Norma S. Nudelman* and Guadalupe E. García Liñares

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P. 3, Ciudad Universitaria, 1428 Buenos Aires, Argentina

Received May 24, 1999

Studies of the reaction of lithium dicyclohexylamide with *N*,*N*-dibutylformamide, 1-formylpiperidine, and 4-formylmorpholine indicate that the equilibria resulting from these compounds are shifted toward the formation of an adduct, which quickly collapses to dicyclohexylamine and the lithiated carbamoyl anion derived from the initial disubstituted formamide. Further reactions of the lithium carbamoyl lead to a new adduct where a lithiated carbon is bounded to N, O, and a carbonyl functionality. The ^{13}C NMR analysis of the reaction mixtures showed the presence of similar intermediates in all cases: adducts of this type have not been reported before. These dilithiated intermediates were trapped with methyl iodide giving the corresponding doubly methylated derivatives. Isolation of substituted glyoxylamides and quantitative determination of the products yields constitute further evidence of the whole reaction scheme proposed.

Introduction

The actual structure of lithiated intermediates generated during organic synthesis and how these structures help to explain the course of the reactions are the subject of active research at present.[1−3] Acyl(formyl)lithium species are key intermediates to afford nucleophilic acylations, and the reaction of organolithium reagents with carbon monoxide provides a fast way for the preparation of a wide diversity of molecules.[4,5] Despite their intensive use in organic synthesis, it is only very recently that an incisive insight into the knowledge of the real nature of intermediate species in solution is being developed.[1,3,6] The knowledge of such species is not only relevant to the mechanisms of the reactions involving it, but it could be constructively used to change the course of those reactions into desired synthetic goals.[2,7,8]

On the other hand, the growing use of lithium bases as reagents for organic and organometallic transformations has led to the realization of the role that aggregation plays in their reactivity and selectivity.[9−12] Consequently, much effort is currently being expended in characterizing their structures both in solution[13] and in the solid state.[14−17] Many complexes are difficult to obtain as single crystals; hence, much of the present knowledge comes from studies using NMR spectroscopy.[18−21]

We have recently synthesized the first adduct, the lithium dimorpholinemethoxide,[3] affording evidence for the first intermediate proposed in the carbonylation of lithium amides, the carbamoyl species $R^1R^2NC(O)Li$. This reaction is very useful for the synthesis of substituted formamides[22] and ureas;[8] the procedure could be also applied for the synthesis of substituted formamides that were recently found to have an antimicrobial activity.[23] These carbonylations have been fully investigated includ-

---

* To whom correspondence should be addressed. Fax: (5411) 576-3346. E-mail: nudelman@qo.fcen.uba.ar.

[1] Ball, S. C.; Cragg-Hine, I.; Davidson, M. G.; Davies, R. P.; Raithby, P. R.; Snaith, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1581.

[2] (a) Müller, A.; Marsch, M.; Harms, K.; Lohrenz, J. C. W.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1518. (b) Stiasny, H. C.; Böhm, V. P. W.; Hoffman, R. W. *Chem. Ver.* **1997**, *130*, 341.

[3] Nudelman, N. S.; Schulz, H.; García Liñares, G.; Bonatti, A.; Boche, G. *Organometallics* **1998**, *17*, 146.

[4] Seyferth, D.; Hui, R. C.; Wang, W. L. *J. Org. Chem.* **1993**, *58*, 5843 and references cited therein.

[5] Nudelman, N. S. Carbonylation of Main-Group Organometal Compounds. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: Chichester, 1989.

[6] Davidson, M. G.; Davies, R. P.; Raithby, P. R.; Snaith, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1695.

[7] Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.

[8] (a) Nudelman, N. S.; Lewkowicz, E. S.; Perez, D. G. *Synthesis* **1990**, 917. (b) Perez, D. G.; Nudelman, N. S. *J. Org. Chem.* **1988**, *53*, 408.

[9] (a) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954. (b) Leung, S. S−W.; Streitwieser, A., *J. Am. Chem. Soc.* **1998**, *120*, 10557. (c) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028.

[10] Henderson, K. W.; Dorigo, A. E.; Williard, P. G.; Bernstein, P. R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1322.

[11] Ball, S. C.; Cragg-Hine, I.; Davidson, M. G.; Davies, R. P.; Edwards, A. J.; Lopez-Solera, I.; Raithby, P. R.; Snaith, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1002.

[12] Reviews on lithium structural chemistry: (a) Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501. (b) Mulvey, R. *Chem. Soc. Rev.* **1991**, *20*, 167.

[13] (a) Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479. (b) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255. (c) Bauer, W. *J. Am. Chem. Soc.* **1996**, *118*, 5450.

[14] Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693.

[15] Boche, G.; Langlotz, I.; Marsch, M.; Harms, K.; Nudelman, N. S. *Angew. Chem., Int. Ed. Engl.* **1992**, *104*, 774.

[16] van Vliet, G. L. J.; de Kanter, F. J. J.; Schakel, M.; Klumpp, G. W.; Spek, A. L.; Lutz, M. *Chem. Eur. J.* **1999**, *5*, 1091.

[17] Clegg, W.; Henderson, K. W.; Horsburgh, L.; Mackenzie, F. M.; Mulvey, R. E. *Chem.—Eur. J.* **1998**, *4*, 53.

[18] (a) Hilmersson, G.; Arvidsson, P. I.; Davidsson, Ö.; Hakansson, M. *J. Am. Chem. Soc.* **1998**, *120*, 8143. (b) Bauer, W. *Magn. Reson. Chem.* **1996**, *34*, 532.

[19] (a) Hüls, D.; Günther, H.; van Koten, G.; Wijkens, P.; Jastrzebski, J. T. B. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2629. (b) Khanjin, N. A.; Menger, F. M. *J. Org. Chem.* **1997**, *62*, 8923.

[20] (a) Aubrecht, K. B.; Collum, D. B. *J. Org. Chem.* **1996**, *61*, 8674. (b) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567.

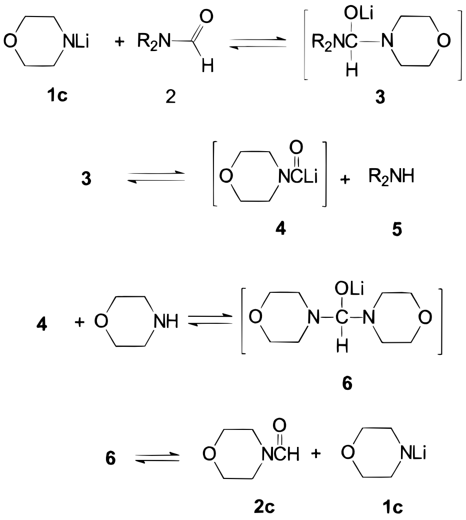
[21] Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042.

[22] (a) Nudelman, N. S; Lewkowicz, E. S.; Furlong, J. P. J. *J. Org. Chem.* **1993**, *58*, 1847. (b) Nudelman, N. S. *Pure Appl. Chem.* **1998**, *70*, 1939.

[23] Dahbi, T. P.; Shah, V. H.; Parikh, A. R. *Indian J. Heterocycl. Chem.* **1992**, *2*(2), 137.

10.1021/jo9908445 CCC: $19.00

Scheme 1



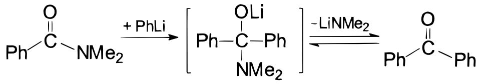
ing the effect of metal catalysts[24,25] and the presence of radical scavengers.[26] The addition of organometallic compounds to disubstituted formamides has been recently applied to the synthesis of *N*,*N*-dialkylaminocyclopropanes.[27]

The specific lithium amide behavior against carbon monoxide provides a useful additional tool for examining the reagent structure in solution;[22] thus, it could be used to predict[8] the formation of an amine–lithium amide mixed dimer. The aggregate was synthesized and its solid-state structure was characterized, the first mixed dimer being reported in the literature.[15] The equilibrium between lithium dialkylamides and the corresponding formamides is a key step in the mechanism of carbonylation since it could explain the dependence of the product distribution on the reaction conditions. Concerning this point, it has been previously observed that acyclic lithium amides behave differently from cyclic ones, and probably they do not form mixed aggregates.[8b,22] Since the presence of an amine plays an essential rol in the capture of the first intermediate[3] (see Scheme 1), it was of crucial interest to study a system in which any mixed aggregates were not involved, to get more insight into the structures and further reactions of the lithium carbamoyl intermediates. We report herein an NMR and GC study of the reaction between lithium dicyclohexylamide and disubstituted formamides.

Results and Discussion

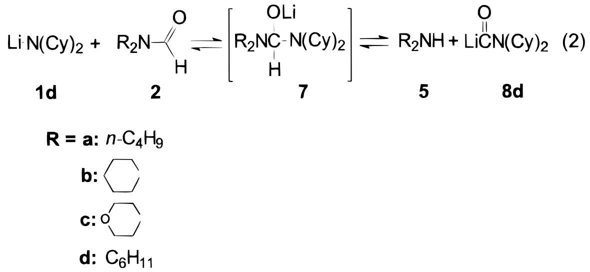
The reaction of lithium morpholide, **1c**, with *N*,*N*-dibutylformamide, **2a**, and 1-formylpiperidine, **2b**, has been previously reported.[3] Protonation reactions and NMR investigations indicate that in the complex equilibria resulting from these compounds the mixed diamino lithium alkoxides, **3**, are formed first (Scheme 1). These intermediates then collapse to the lithium morpholide carbamoyl anion species, **4**, and the corresponding amines, **5**. **4** reacts with morpholine to give finally the lithium dimorpholinemethoxide, **6**, which was detected by ^{13}C NMR. An adduct like **6**, which can be considered as an adduct of an amide with lithium amide, had not been characterized yet.[5]

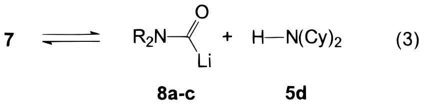
Shortly after, the first adduct between an amine and a carbonyl derivative was isolated in the solid state by the reaction of *N*,*N*-dimethylbenzamide with phenyllithium in diethyl ether (eq 1).[28] The tetrahedral structure of the adduct was fully characterized; it is of fundamental interest as a model for the "in vivo" acylation reactions,[29] and because it shows a structure consistent with the Dunitz trajectory in the addition of an amine nucleophile to a carbonyl group toward a tetrahedral intermediate.[30]



(1)

In the present case, a system is chosen to study further reaction of the first carbonylation adduct to a second intermediate that allowed characterization of the nature and structures of the species in solution. Thus, the reaction of lithium dicyclohexylamide, **1d**, with *N*,*N*-dibutylformamide, **2a**, 1-formylpiperidine, **2b**, and 4-formylmorpholine, **2c**, was studied in THF at room temperature using equimolar quantities of the reactants (see eq 2). **1d** was chosen for this study, in which complex equilibria were expected, since it is one of the less acidic lithium amide–amine pairs,[31] and the four species involved in the equilibria with some other amides in THF could be easily recognized by ^{13}C NMR.[31] The reaction was initiated by mixing 2.0 mL of a 1 M solution of **1d** in THF with the corresponding neat formamide and then allowed to react for 15 min before quenching with saturated NH_4Cl solution. The reaction mixture was analyzed by gas chromatography; surprisingly, in all cases the main product was dicyclohexylamine, **5d**. The





---

(24) Nudelman, N. S.; García Liñares, G.; Schulz, H. *Main Group Metal Chem.* **1995**, *18*, 147.

(25) (a) McCusker, J. E.; Abboud, K. A.; McElwee-White, L. *Organometallics* **1997**, *16*, 3863. (b) Rülke, R. E.; Dolis, J. G. P.; Grost, A. M.; Elsevier: C. J.; Van Leeuween, P. W. N. M.; Vrieze, K.; Goubitz, K.; Schenk, H. *J. Organomet. Chem.* **1996**, *511*, 47.

(26) (a) Nudelman, N. S.; Doctorovich, F., García Liñares, G.; Schulz, H. *Gazz. Chim. Ital.* **1996**, *126*, 19. (b) Nudelman, N. S.; García Liñares, G. *An. Asoc. Quim. Arg.* **1996**, 619.

(27) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413.

(28) Adler, M.; Marsch, M.; Nudelman, N. S.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1261.

(29) (a) Smith, R. M.; Hansen, D. E. *J. Am. Chem. Soc.* **1998**, *120*, 8910. (b) Venturini, A.; López-Ortiz, F.; Alvarez, J. M.; González, J. *J. Am. Chem. Soc.* **1998**, *120*, 1110. (c) Adalsteinsson, H.; Bruice, T. C. *J. Am. Chem. Soc.* **1998**, *120*, 3440.

(30) (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956.

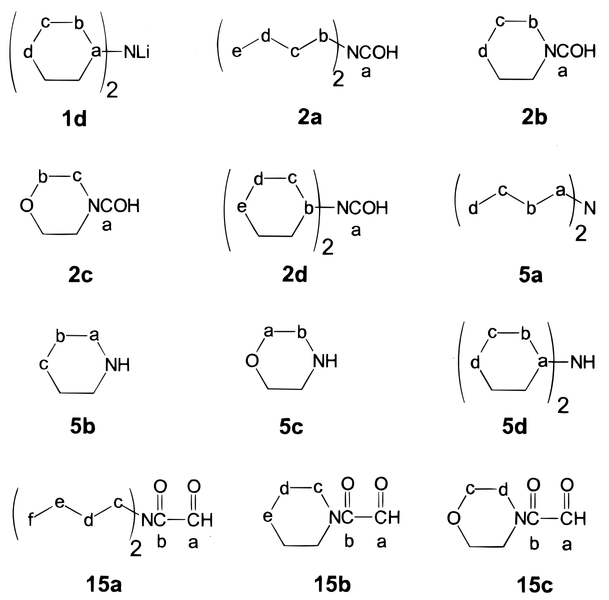
(31) Furlong, J. J. P.; Lewkowicz, E. S.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1461.

Table 1. ^{13}C NMR Shifts of the Individual Species[a]

compd	C_a	C_b	C_c	C_d	C_e	C_f
1	62.3	40.1	27.6	27.6		
2a	161.9	46.7/41.6	31.3/29.9	20.5/19.9	13.7/13.5	
2b	160.3	46.3/40.2	27.0/25.8	25.6/25.1		
2c	160.2	67.5/66.6[b]	45.8/40.7			
2d	162.5	47.1/40.9	32.3/31.1	26.7/26.3	26.3/26.1	
6a	50.0	32.7	20.8	14.0		
6b	47.6	27.4	25.8			
6c	68.3	47.2				
6d	53.2	34.9	26.8	25.4		
15a	189.0	157.2	47.5/45.2	30.8	20.2	13.7
15b	187.1	155.6	46.5/44.0	24.4	25.5	
15c	187.0	155.3	66.8	44.4/41.8		

[a] δ_C/ppm; THF−C_6D_6 (5:1). [b] Under the signal corresponding to α-C of THF.

Chart 1



retention times of the other products corresponded to the formamides **2**(**a**−**d**) and the amines derived from the initial formamides **5**(**a**−**c**).

In principle, these products could be explained by eqs 2 and 3. Thus, similarly to Scheme 1, lithium dicyclohexylamide **1d** and a substituted formamide **2** would form an adduct **7** (eq 2), which would collapse to dicyclohexylamine **5d** and the lithium carbamoyl species, **8a**−**c**, derived from formamide (eq 3). The lithium carbamoyl, **8**, had been previously called to be an "island of stability in the area of acyl anions".[32] Nevertheless, we have previously demonstrated that it is a highly reactive intermediate, and it is unlikely that it could survive unchanged in the reaction mixture.[8]

^{13}C NMR Spectra Evidence of Intermediates. To know more about the real nature of the intermediates before hydrolysis, the different reaction mixtures were analyzed by ^{13}C NMR. The NMR shifts of the individual species are given in Table 1, the assignments corresponding to the carbons as labeled in Chart 1. As it is known, the amide functional group is characterized by some specific properties such as coplanarity of the groups attached to the nitrogen atom and substantial rotational barrier. These properties are readily rationalized with the concept of the amide resonance, whose the most general definition is the ability of the nitrogen atom to delocalize its lone pair over the whole C,N,O π system so as to gain stabilization.[33] Hence, in the case of the disubstituted formamides **2**, both alkyl groups are not equivalent, which leads to two signals for each type of carbon (see shifts for C_b−C_e separated by slashes in Table 1). This feature of the amide functionality was then useful to characterize the new reaction intermediates.

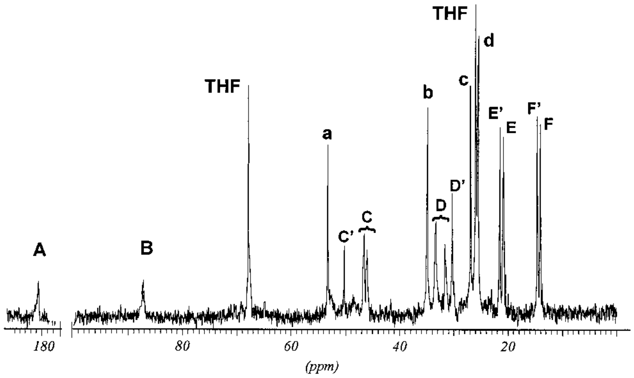


Figure 1. ^{13}C NMR spectrum in THF−C_6D_6 (5:1) of the reaction mixture of lithium dicyclohexylamide, **1d**, with *N*,*N*-dibutylformamide, **2a**. The signals labeled a−d correspond to the carbons in compound **5d**; the signals marked A−F and C′−F′ correspond to the carbons in compound **9a**.

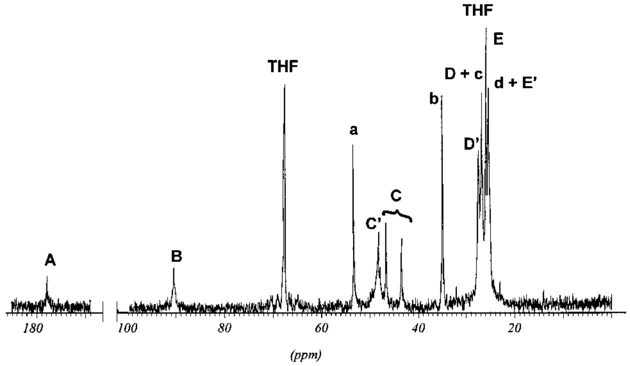


Figure 2. ^{13}C NMR spectrum in THF−C_6D_6 (5:1) of the reaction mixture of lithium dicyclohexylamide, **1d**, with 1-formylpiperidine, **2b**. The signals labeled a−d correspond to the carbons in compound **5d**; the signals marked A−E and C′−E′ correspond to the carbons in compound **9b**.

The ^{13}C NMR spectrum of the reaction mixture of lithium dicyclohexylamide with *N*,*N*-dibutylformamide, **1d** + **2a** (see Figure 1), shows a set of signals in which those due to the a−d carbons of dicyclohexylamine **5d** are clearly recognized, together with another set of 10 peaks that are marked A−F and C′−F′ in the spectrum. Similarly, Figure 2 shows the ^{13}C NMR spectrum of the reaction mixture of **1** + **2b**; one observes the presence of peaks due to the a−d carbons of **5d** together with other eight peaks (A−E, C′−E′). The spectrum of **1d** + **2c** shows again the signals for **5d** and other six peaks (A−D, C′−D′) (Figure 3). In any case, signals for the original dialkylformamides **2** or for the corresponding dialkylamines **5** were observed.

The lithium carbamoyl **8**, as a highly reactive intermediate, can add to another moiety of **8** forming a new

---

[32] Rautenstrauch, V.; Joyeaux, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 83.

[33] (a) Lauvergnat, D.; Hiberty, P. C. *J. Am. Chem. Soc.* **1997**, *119*, 9478. (b) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201.

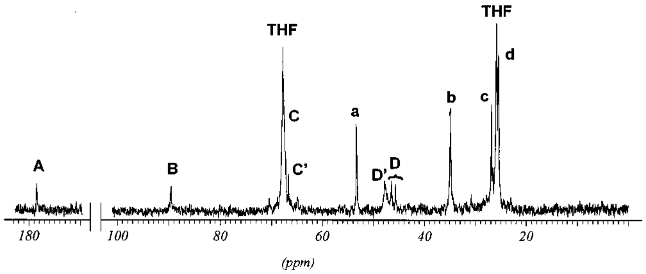


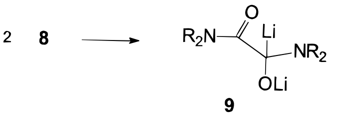
Figure 3. ^{13}C NMR spectrum in THF$-$C$_6$D$_6$ (5:1) of the reaction mixture of lithium dicyclohexylamide, **1d**, with 1-formylmorpholine, **2c**. The signals labeled a$-$d correspond to the carbons in compound **5d**; the signals marked A$-$D and C′$-$D′ correspond to the carbons in compound **9c**.

Table 2. ^{13}C NMR Shifts of the Intermediates and Reaction Products[a]

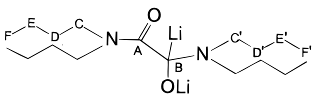
compd	C$_A$	C$_B$	C$_C$	C$_{C'}$	C$_D$	C$_{D'}$	C$_E$	C$_{E'}$
9a[b]	180.4	87.5	46.5/46.0	50.1	33.3/31.6	30.3	20.9	21.5
9b	178.6	90.4	46.6/43.4	48.3	27.5/26.8	26.8	25.9	25.5
9c	179.0	89.5	67.7/67.4	65.0	46.4/45.6	47.7		
11	59.9	32.3	26.3		26.2		43.7	
12a[c]	164.8	70.6	51.0		24.5		47.6/45.3	49.6
12b[d]	169.0	83.7	59.5		24.8		48.9/40.9	49.3
12c[e]	170.6	82.9	55.9		25.3		70.5/67.1	65.7

[a] δ_C/ppm; THF$-$C$_6$D$_6$ (5:1). [b]Additional signals: C$_F$, 14.1; C$_{F'}$, 14.6. [c]Additional signals: C$_F$, 30.4/29.7; C$_G$, 20.5; C$_H$, 13.9; C$_{F'}$, 32.2; C$_{G'}$, 20.7; C$_{H'}$, 13.8. [d]Additional signals: C$_F$, 26.7/25.4; C$_G$, 24.6; C$_{F'}$, 25.8; C$_{G'}$, 24.6. [e]Additional signals: C$_F$, 45.4; C$_{F'}$, 48.0.

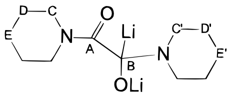
adduct **9** (eq 4). In fact, the ^{13}C NMR spectrum (Table 2) of each reaction mixture before hydrolysis (Figures 1$-$3) suggests the formation of a similar intermediate, **9**, in all three cases. Table 2 shows the most relevant ^{13}C NMR signals for some intermediates and reaction products. In the three cases, signals for both a carbonyl carbon and for a tetrahedral highly deprotected carbon are observed, which correspond to the C$_A$ and C$_B$ of intermediate **9**; the rest of the signals in each case correspond to the alkyl group carbons (e.g., compare the signals with the corresponding peaks for compounds **2** in Table 1).



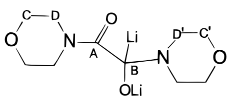
(4)



9a



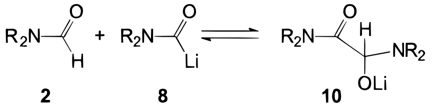
9b



9c

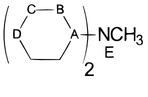
Intermediates of the type **9** are of great interest, and recent work has concentrated on isolating and characterizing lithium intermediates that occur during “one-pot” organic synthesis involving lithium reagents.[34] Of particular interest is the intermediacy of dilithiated organic molecules. Although such species are often proposed to be present prior to workup in numerous organic syntheses, it is difficult to obtain solid dilithiated compounds.[34,35] To the best of our knowledge, this is the first time that an entity with a lithiated carbon bonded to N, O, and a carbonyl functionality is described.

The lithium carbamoyl **8** can also add to unreacted formamide to give another monolithiated intermediate **10** (eq 5), whose NMR signals would be very similar to those of intermediate **9**. Searching evidences for **9**, the hydrogen-coupled ^{13}C NMR spectra of the each reaction mixture were determined, and they showed a doublet plus a singlet for the signal corresponding to C$_B$ (see the Supporting Information). This suggests that indeed both **9** (singlet for C$_B$) and **10** (doublet for C$_B$) intermediates exist in the reaction mixture.

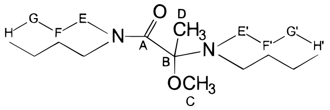


(5)

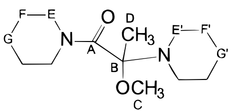
To prove that the signals in the ^{13}C NMR spectra (Figures 1$-$3) indeed correspond to the proposed dilithiated intermediate **9**, an electrophile (methyl iodide) was added to each reaction mixture to trap the intermediate. The reaction mixture was analyzed by ^{13}C NMR, GC, and GC$-$MS. The NMR analysis showed in all cases the presence of dicyclohexylamine, *N*-methyldicyclohexylamine **11**, and a set of signals corresponding to compounds **12**, which are the doubly methylated derivatives of the dilithiated adducts **9**. GC$-$MS analysis of the reaction mixture, showed also the presence of the monomethylated derivatives of the intermediates **10**, compounds **13**. This constitutes additional evidence that **9** is the proposed intermediate discussed above and that **10**, obtained by addition of carbamoyl species to unreacted formamide, is also in the reaction mixture. The ^{13}C NMR shifts of compounds **12** are also shown in Table 2. It is worthy of note that **11** was obtained in the presence of methyl iodide even though the NMR spectrum showed that lithium dicyclohexylamide was not present in the reaction mixture. Thus, the reaction between dicyclohexylamine and iodomethane was independently carried out in THF giving, after 30 min, *N*-methyldicyclohexylamine, **11**, in 80% yield.



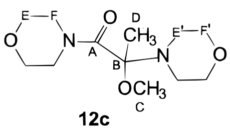
11



12a



12b



12c

We have recently shown by “ab initio” theoretical calculations that carbamoyl intermediates of type **8** have, in fact, a “carbene-like” structure.[36] The chemistry of carbenes has received increasing interest since Ar-

---

(34) Ball, S. C.; Cragg-Hine, I.; Davidson, M. G.; Davies, R. P.; Edwards, A. J.; Lopez-Solera, I.; Raithby, P. R.; Snaith, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 921.

(35) Ball, S. C.; Cobb, J.; Davies, R. P.; Raithby, P. R.; Shields, G. P.; Snaith, R. *J. Organomet. Chem.* **1997**, *534*, 241.

(36) Viruela-Martin, P.; Viruela-Martin, R.; Tomas, F.; Nudelman, N. S. *J. Am. Chem. Soc.* **1994**, *116*, 10110.

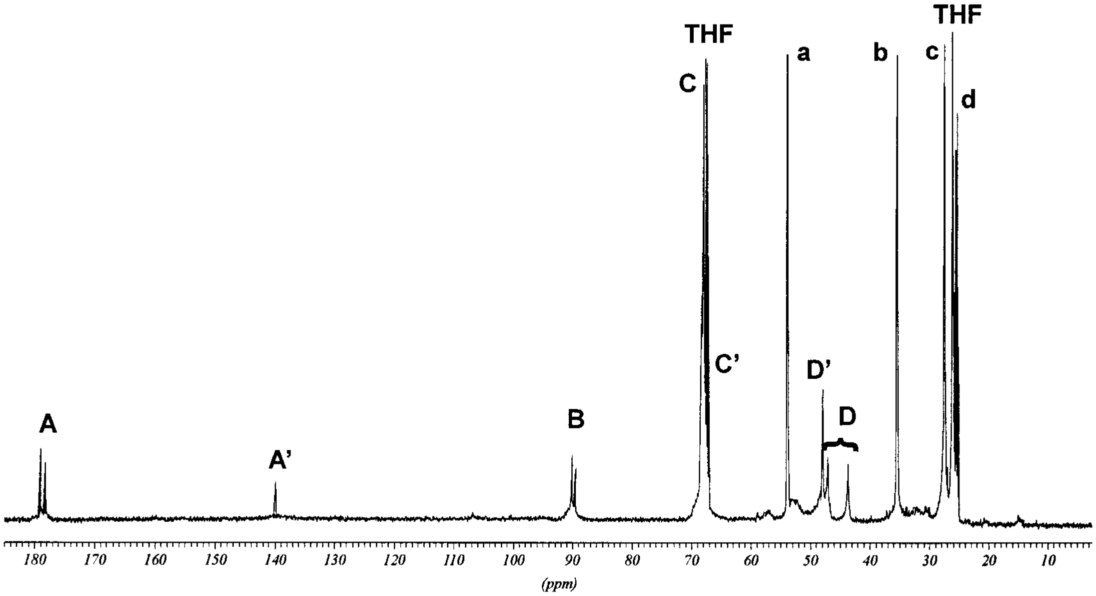
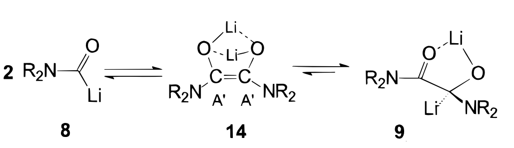


Figure 4. ^{13}C NMR spectrum 500 MHz in THF-d_8 of the reaction mixture of lithium dicyclohexylamide, **1d**, with 1-formylmorpholine, **2c**. The signals labeled a−d correspond to the carbons in compound **5d**; the signals marked A−D and C′−D′ correspond to the carbons in compound **9c** and **10c**, and the signal marked A′ correspond to $C_{A'}$ in intermediate **14c**.

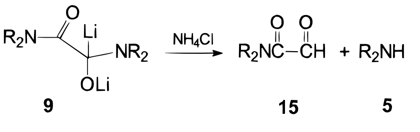
duengo[37] determined the first structure of a carbene, and active research is being carried out at present.[38,39] Coupling is one of the most typical reactions of carbene intermediates; if the carbamoyl species **8** has an oxycarbene structure, we should find some evidence of the coupling product, **14** (eq 6). However, in the NMR spectra of each reaction mixture there is any signal that could be assigned to $C_{A'}$. The ^{13}C NMR spectra were then determined in a Bruker 500 MHz spectrometer; sensitivity enhancement allowed to reveal a signal around 140−142 ppm, which would correspond to the C=C of the intermediate proposed, **14** (see Figure 4; other spectra are in the Supporting Information). This result confirms the presence of **14** in the reaction mixture, in small amounts since **8** is rapidly consumed to form **9** and **10**. In fact, once the location of the peak was determined from the higher field spectra, the reaction between lithium dicyclohexylamide and *N*,*N*-dibutylformamide carried out at higher concentration showed a small signal around 140 ppm in the ^{13}C NMR 200 MHz spectrum (see the Supporting Information).



(6)

On the other hand, in the ^{13}C NMR 500 MHz spectra, the signals around 178 and 90 ppm corresponding to C_A and C_B, respectively, of **9** and **10** appeared as two peaks in each case, which is a further evidence of the existence of the two intermediates, mono- and dilithiated, that now, under higher resolution, are shown as two differentiated signals in each case (see Figure 4).

Quantitative GC Analysis of the Reaction Mixtures. In light of the above results, if species **9** and **10** are the real intermediates in the reaction mixtures, they would produce, by hydrolysis, double carbonylated compounds: in both cases, dialkyl-substituted glyoxylamide, **15**, and the corresponding amine, **5**, should be the products (eq 7). The dialkyl-substituted glyoxylamides **15(a−c)** were independently prepared, and they showed to have exactly the same retention times that the corresponding dialkylformamides under the GC conditions used in the present work. Isolation and characterization of the reaction products showed that glyoxylamides **15** were the main carbonylated products in the reaction mixture, while formamides **2** were in minor amounts ([**15**]:[**2**] ≅ 4). Further quantitative analysis by gas chromatography shed new light on the complex system, and the relative proportions of each products were fully consistent with the proposed reaction mechanism shown in Scheme 2. As was stated at the beginning of these section, in all cases the main product was, surprisingly, dicyclohexylamine **5d**; the complete results are summarized in Table 3.



(7)

The reaction of **1d** and **2** gives the tetrahedral intermediate **7**; a small amount of it (nearly 0.2 mmol) collapses to the corresponding lithium amide and dicyclohexylformamide, **2d** (eq 2). Nevertheless, because of the less acidic character of dicyclohexylamine,[31] the main proportion collapses to give equimolar amounts of dicyclohexylamine (main product, 1.8−1.9 mmol) and the lithium carbamoyl, **8** (eq 3). Further reaction of two molecules of **8** (and of **8** + **2**), produces intermediate **9** (and **10**), to give 0.8−0.9 mmol of the main carbonylated product, **15**, and similar amounts of the corresponding dialkylamine. The results shown in Table 3 are fully consistent with these reactions.

---

(37) (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(38) Boche, G.; Marsch, M.; Müller, A.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1032.

(39) (a) Zuev, P. S.; Sheridan, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 4123. (b) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530. (c) Arduengo, A. J., III; Dias, H. V. R.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1992**, *114*, 9724.

Scheme 2

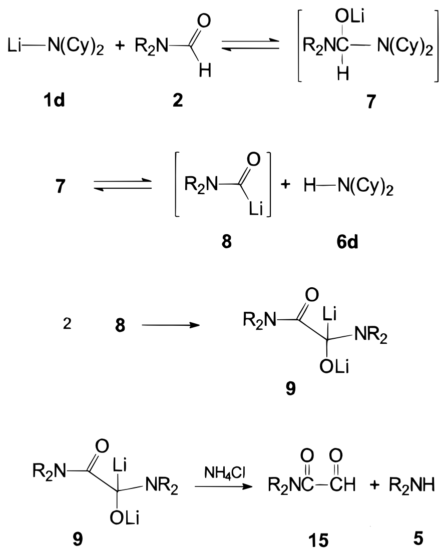


Table 3. Reaction of Lithium Dicyclohexylamide, 1d, with Disubstituted Formamides[a]

products\formamide	6a	6b	6c	6d	15a	15b	15c
N,*N*-dibutylformamide	1.0			1.8	0.9[b]		
1-formylpiperidine		1.0		1.9		0.8[b]	
4-formylmorpholine			1.0	1.8			0.9[b]

[a] Amounts of products (in mmoles) determined by GC after hydrolysis. 2 mmol of each reactant was initially present in the reaction mixture. [b] In all cases ≤ 0.2 mmol of dicyclohexylformamide and ≤ 0.2 mmol of the original formamide were also obtained.

Quantitative GC analysis of the reaction mixture after treatment with methyl iodide affords further evidence of the proposed reaction scheme. Thus, GC−MS analysis showed the presence of dicyclohexylamine **5d** (0.6 mmol), *N*-methyldicyclohexylamine **11** (1.2 mmol), the doubly methylated derivatives of the intermediate **9**, **12** (0.6 mmol), the amine corresponding to the initial formamide **5a**−**c** (0.5 mmol), and glyoxylamide **15a**−**c** (0.4 mmol), plus small amounts of the original formamide **2a**−**c** (0.2 mmol), *N*,*N*-dicyclohexylformamide **2d** (0.2 mmol), and the monomethylated derivatives **13** of the intermediate **10** (approximately 0.2 mmol).

Conclusions

It is shown by ^{13}C NMR and GC investigations that the reaction between lithium dicyclohexylamide **1d** and *N*,*N*-dibutylformamide **2a**, 1-formylpiperidine **2b**, and 4-formylmorpholine **2c**, respectively, produces mainly a dilithiated intermediate in which a lithiated carbon atom is bonded to N, O, and a carbonyl functionality. To the best of our knowledge, such an entity has not been described before; it is of fundamental interest to show the real nature of carbonylation and other reaction intermediates, as well as a model for tetrahedral adducts of biological interest. The reaction between **1d** and **2,** gives the first adduct **7**, which collapses via proton transfer to give dicyclohexylamine, **5d**, and a lithiated carbamoyl species, **8**; further reactions of **8** give the dilithiated intermediate, **9**, which could be trapped with methyl iodide. The results show that the product yield after hydrolysis does not reflect the real situation in the reaction mixture; this emphasizes the significance of ^{13}C NMR investigations to get more insight into the nature of the intermediates and the mechanisms of reaction when organolithium reagents are involved.

Experimental Section

General Comments. All reactions involving organolithium reagents were carried out by standard techniques for the manipulation of air- and water-sensitive compounds.[40] Distilled THF was refluxed over sodium benzophenone ketyl until a dark blue solution was obtained and then distilled immediately before use under dry oxygen-free nitrogen. Commercial dialkylamines were left over sodium strings for several days, refluxed and distilled over sodium, and then kept under nitrogen in sealed ampules, which were opened immediately prior to use. ***n*-Butyllithium** was prepared by cutting lithium wire (4.6 g, 1 mol) in small pieces into a flask containing boiling hexane (250 mL); the flask was capped with a nonair stopper and kept at 54−58 °C. Butyl chloride (31.3 mL, 1 mol) was syringed in small aliquots into the flask during 3 h and the mixture left to react for 1 h at 55 °C. **Lithium dicyclohexylamide (1d):** cooled (0 °C) *n*-BuLi (2.5 mL, 0.8 M in hexane) was syringed into a nonair stopper capped tube under nitrogen atmosphere, and the freshly distilled dicyclohexylamine (2 mmol) was added. The white lithium amide precipitate was worked up as previously described.[8b]

***N*,*N*-Dialkylformamides (2).** Ten grams of the corresponding amine was added in aliquots into a flask containing 10 g of cooled (0 °C) formic acid. The salt formed solidified and melted on heating. The corresponding formamide was purified by distillation (yield 75%): **2a**, bp 235 °C; **2b**, bp 221 °C; **2c**, bp 237 °C; **2d** was purified by recrystallization: mp 61 °C.

***N*,*N*-Dialkylglyoxylamides (15).** Compounds **15** were prepared by reductive ozonolysis of the diethyl tartrate in methanol, followed by amidation and hydrolysis as previously described (yield 65%).[8b] **15d**: mp 115−117 °C (hexane); the structure was confirmed by X-ray analysis.[41] See ^{13}C NMR in Table 1. **15a** was synthesized by carbonylation: a lithium amide solution (0.5 M) in THF/HMPT (1:1) at 0 °C was exposed to carbon monoxide at ca. 1013 mbar. Once the reaction was completed, the solution was treated twice with H_3PO_4 (5%) and washed with $NaHCO_3$ and water. The organic layer was dried, and distillation of the solvent rendered a vitreous mass (yield > 90%). See ^{13}C NMR in Table 1.

Reaction between Lithium Dicyclohexylamide, 1d, and Substituted Formamides, 2. A 2.0 mmol portion of **1** was dissolved in 2 mL of anhydrous THF in a nonair stopper capped tube; 2.0 mmol of the corresponding neat formamide was then added and allowed to react for 15 min before addition of saturated NH_4Cl solution. In the trapping reactions, methyl iodide (shaked with $NaHSO_3$ and passed through a column of alumine oxide) was used instead of saturated NH_4Cl solution.

Reaction between Dicyclohexylamine and Methyl Iodide. A 5.0 mmol portion of methyl iodide was added to 5 mL of a 1.0 M solution of dicyclohexylamine (**5d**) in THF at room temperature. After 5 min, a yellow solid precipitated. The reaction mixture was kept at 25 °C for 30 min, after which time the solid was filtered (mp 194−196 °C).

^{13}C NMR Measurements. ^{13}C NMR spectra of THF/C_6D_6 (5:1) or THF-d_8 solutions of all the involved amines, formamides, and lithium amides were recorded in a Bruker 200 spectrometer. In all cases, shifts were determined with respect to the central signal corresponding to deuterated benzene ($\delta = 128.000$ ppm) or Cα of THF-d_8 ($\delta = 67.700$ ppm). The spectra of the lithium amide/formamide mixtures were determined as follows: 0.5 mL of a 1.0 M solution of lithium dicyclohexylamide (**1**) were syringed into a nitrogen-filled NMR tube capped with a septum. An equimolar amount of the corresponding formamide, **2**, was syringed into the tube at room temperature and shaked manually (in all cases some heating of the solution

---

(40) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; Wiley: New York, 1986.

(41) Nudelman, N. S.; Pérez, D.; Galloy, J.; Watson, W. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1983**, *C39*, 393.

was observed). After 15 min, 1000–2000 scans of proton-decoupled ^{13}C spectra were accumulated.

Acknowledgment. G.G.L. is grateful for a fellowship from the University of Buenos Aires (UBA). The authors are indebted to LANAIS CONICET RMN 500 for the ^{13}C NMR 500 MHz spectra. Financial support from UBA, the National Research Council (CONICET), and the Agency for the Promotion of Science and Technology of Argentina and from the European Community are acknowledged.

Supporting Information Available: Copies of ^{13}C NMR spectra 500 MHz and hydrogen-coupled ^{13}C NMR spectra of the reactions mixtures **1d** + **2a**, **1d** + **2b**, and **1d** + **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9908445